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(19)

(54) PHARMACEUTICAL COMPOSITION

(71) We, THE PROCTER & GAMBLE COMPANY, a company organised under the laws of the State of Ohio, United States of America, of 301 East Sixth Street, Cincinnati, Ohio 45202, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to compositions and methods for treating the anomalous mobilization and deposition of calcium phosphate salts in animal tissues. More specifically, organophosphonate compounds are combined with organosulfoxides to provide compositions especially adapted to be administered topically to the afflicted situs in subjects suffering from a variety of disease states involving the abnormal metabolism of bone mineral.

A number of pathological conditions which can afflict warm-blooded animals involve abnormal calcium and phosphate metabolism. Such conditions are generally characterized by the anomalous mobilization of calcium and phosphate leading to general or specific bone loss, and the anomalous deposition of calcium phosphate salts in body tissues, i.e., pathological calcification. Such disease states include osteoporosis, osteitis deformans, various other conditions with a calcification component such as myositis ossificans progressivea, scleroderma, calcification in the hip from introduction of a prosthetic device, and recalcification of an area following surgical removal of existing calcification, as well as afflictions such as arthritis, neuritis, bursitis, tendonitis, and other inflammatory conditions which predispose the involved tissue to the deposition of calcium phosphates. Frank deposition of bone mineral at joints, along the skeleton, and in soft tissues, with attendant pain and loss of function, is characteristic of these disease states. Such afflictions are usually progressively debilitating.

The systemic administration of organophosphonate compounds of the type described hereinafter has been reported to be an effective treatment for disease states involving abnormal metabolism of bone mineral and pathological calcification. By the present invention, it has been discovered that the organophosphonates can be caused to penetrate through the skin and soft tissues directly to the site of pathological calcification. This desirable penetration effect is obtained by the use of organosulfoxide compounds of the type disclosed hereinafter. Accordingly, direct treatment of the afflicted situs, with attendant diminution of potential side-effects caused by systemic administration of the organophosphonate compounds is now possible.

The use of solvent concentrations of dimethyl sulfoxide (DMSO) to promote skin penetration of certain drugs is known in the scientific and non-technical literature.

U.S. Patent 3,527,864, discloses the use of the organosulfoxides used in this invention to promote the penetration of certain drug agents through the skin.

U.S. Patent 3,896,238, discloses the use of organosulfoxides in combination with sugar esters to promote the penetration of certain drug agents through the skin.

The phosphonate compounds used in the practice of this invention are reported in the literature as being useful in the treatment of anomalous mobilization and deposition of calcium phosphate salts (bone mineral) in humans and other animals. See especially the U.S. Patents 3,683,080; 3,678,164; 3,662,066; 3,553,314; 3,553,315; 3,584,124; 3,584,125 and 3,641,246.

The article by Francis, Floro and King, entitled "The Effects of Disodium Ethane-1-Hydroxy-1,1-Diphosphonate on Adjuvant Induced Arthritis in Rats", appearing in *Calc. Tiss. Res 9*, 109—121 (1972) mentions the use of phosphonates to inhibit inflammatory erosion of cartilage in rats.

Detergent compositions comprising organophosphonate materials to sequester water hardness cations and organosulfoxides as the detersive surfactant, but containing as essential ingredients components or being in a form which precludes their use for topical pharmaceutical treatment, are disclosed in several United States Patents, including: 3,502,585; 3,526,592; 3,351,558, and references cited therein.

In spite of the substantial body of literature relating to the components of the present invention, medicinal compositions which comprise combinations of organophosphonates and organosulfoxides and their utility as topical treatments to alleviate or prevent pathological calcification do not appear to have been appreciated heretofore.

The present invention is directed to compositions and methods for treating anomalous mobilization and deposition of calcium phosphate salts (bone mineral) and attendant inflammation of pain in the tissues of humans and lower animals. Disease states such as Paget's Disease *(osteitis deformans)*, myositis ossificans progressiva, osteoporosis, arthritis, bursitis, and other maladies involving heterotopic calcification can be treated in the manner of this invention. In contrast with prior art treatments with organophosphonates which involve systemic administration of the drug, the present invention employs a penetrating carrier for the organophosphonate drug which allows direct, topical application to the afflicted situs.

The present invention encompasses compositions especially adapted for the topical treatment of anomalous mobilization and deposition of calcium phosphate salts in the tissues of humans and lower animals, comprising:

i) a safe and effective amount of an organophosphonate compound; and

ii) a carrier which comprises a safe and effective amount of an organosulfoxide compound, and in which the composition is fluid (as hereinafter defined) and has a pH in aqueous solution of not less than 3.5 nor more than 10.0.

The present invention also encompasses a method for treating or preventing the anomalous mobilization and deposition of calcium phosphate salts in the tissues of humans and lower animals in need of such treatment, comprising topically applying thereto, at the afflicted situs, a safe and effective amount of a composition of the foregoing type.

The compositions herein comprise a safe and effective amount of an organophosphonate compound in combination with a carrier which comprises a safe and effective amount of an organosulfoxide compound. The carrier and organophosphonate compound are selected from pharmaceutically-acceptable, compatible materials which, when combined, provide penetrating liquid compositions especially adapted for topical application to an afflicted situs.

By "safe and effective amount of organophosphonate compound" herein is meant a sufficient amount of the organophosphonate compound to alleviate pathological calcification at a reasonable benefit/risk ratio attendant with any medical treatment. Within the scope of sound medical judgment, the dosage of organophosphonate will vary with the particular condition being treated, the severity of the condition, the duration of the treatment, and the specific organophosphonate employed.

By "carrier" herein is meant a liquid or fluid material comprising the organosulfoxide dissolved therein or therewith, which dissolves the organophosphonate compound and remains in the liquid or fluid state.

By "safe and effective amount of organosulphoxide compound" herein is meant sufficient organosulfoxide compound to provide penetration of the organophosphonate compound through the epidermal barrier to the afflicted situs without unacceptable side effects.

By "pharmaceutically-acceptable" herein is meant that the ingredients are suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio.

By "compatible" herein is meant that the components of the compositions are capable of being commingled without interacting in a manner which would substantially decrease the efficacy of the total compositions under ordinary use situations.

By "topical application" herein is meant directly laying on or spreading on epidermal tissue (including outer skin and oral, gingival, nasal, etc. tissue).

By "afflicted situs" herein is meant the localized area of pathological calcification, and the immediate surrounding area.

All percentages herein are by weight, unless other wise specified.

The organophosphonate compounds and organosulfoxide compounds critical to the practice of this invention are discussed more fully hereinafter. Optional ingredients which can be included in the compositions to provide aesthetic and cosmetic benefits, but which are not critical to the practice of the invention, are also disclosed hereinafter.

The organophosphonate compounds (or, more succinctly, "phosphonates") employed in the manner of this invention are of the type discussed hereinafter.

The phosphonate compounds which can be employed in the present invention are characterized by the phosphonate moiety ($-PO_3M_2$, wherein M represents H or a pharmaceutically-acceptable cation or ester group. The phosphonates herein are organophosphonates, i.e., the phosphonate moiety is attached to a carbon atom by a carbon-phosphorus bond (C—P bond). The carbon atoms, in turn, is bonded to other hydrocarbyl groups, e.g., alkyl phosphonates, or to hydrogen atoms, e.g., methane phosphonates, or to mixed hydrocarbyl groups, hydrogen atoms or other substituents, e.g. haloalkyl phosphonates. The hydrocarbyl groups can be substituted or non-substituted alkyl (including cycloalkyl) and aryl (including heteroaryl). Substituent groups on the alkyl or aryl hydrocarbyl moiety can be, for example, additional phosphonate moieties; halogens, especially chlorine; carboxyl; esterified carboxyl; hydroxyl; amino and amido. Preferred for use herein are organophosphonates having more that one $C-PO_3M_2$ group; diphosphonates, especially geminal diphosphonates characterized by the grouping

$$(M_2O_3P-\underset{|}{\overset{|}{C}}-PO_3M_2)$$

are most highly preferred.

Typical phosphonate compounds useful herein are of the formula

(I) $R_1-\underset{|}{\overset{R}{(C)_n}}-R_2$; (vicinal) and (II) $R_3-\underset{|}{\overset{PO_3H_2}{(C)_n}}-R_4$ (geminal)

wherein n is an integer from 1 to 10 and the substituent groups are H, alkyl, aryl and alkenyl. Examples of type I phosphonates are those wherein R, R_1 and R_2 are each hydrogen, alkyl, $-CH_2OH$ or are as noted for groups R_3 and R_4. Examples of type II phosphonates are those wherein R_3 is hydrogen, alkyl containing from 1 to about 20 carbon atoms, alkenyl containing from 2 to about 20 carbon atoms, aryl (e.g., phenyl and naphthyl), phenylethenyl, benzyl, halogen (e.g., chlorine bromine, and fluorine), amino, substituted amino (e.g., dimethylamino, diethylamino, N-hydroxy-N-ethylamino, acetylamino), $-CH_2COOH$, $-CH_2PO_3H_2$, $-CH(PO_3H_2)(OH)$ or $-CH_2CH(PO_3H_2)_2$; R_4 is hydrogen, lower alkyl (e.g., methyl, ethyl, propyl, and butyl), amino, benzyl, halogen (e.g., chlorine, bromine and fluorine) hydroxyl, $-CH_2COOH$, $-CH_2PO_3H_2$, or $-CH_2CH_2PO_3H_2$, or a pharmaceutically-acceptable salt thereof such as alkali metal (e.g., sodium and potassium), alkaline earth metal (e.g., calcium and magnesium), non-toxic heavy metal (e.g., stannous and indium), and ammonium or low molecular weight substituted ammonium (e.g., mono-, di-, and tri-ethanolammonium) salts. It will be appreciated that groups R, R_1 and R_2 and groups R_3 and R_4 can be cycloalkyl heterocyclic or can be joined in ring structures, said rings being carbocyclic or heterocyclic.

The above described organophosphonic acids and their pharmaceutically-acceptable salts and esters are commonly referred to collectively as "phosphonates", "diphosphonates" or "polyphosphonates".

Operable phosphonates of the above formula (I) include propane-1,2,3-tri-

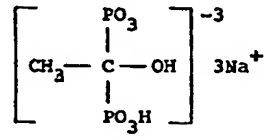
phosphonic acid; butane-1,2,3,4-tetraphosphonic acid; hexane-1,2,3,4,5,6-hexaphosphonic acid; hexane-1-hydroxy-2,3,4,5,6-pentaphosphonic acid; hexane-1,6-dihydroxy-2,3,4,5-tetraphosphonic acid; pentane-1,2,3,4,5-pentaphosphonic acid; heptane-1,2,3,4,5,6,7-heptaphosphonic acid; octane-1,2,3,4,5,6,7,8-octaphosphonic acid; nonane-1,2,3,4,5,6,7,8,9-nonaphosphonic acid; decane-1,2,3,4,5,6,7,8,9,10-decaphosphonic acid; and the pharmaceutically acceptable salts of these acids, e.g., sodium, potassium, calcium, magnesium, ammonium, triethanolammonium, diethanolammonium, and monoethanolammonium salts.

Among the operable phosphonates encompassed by the above formula (II) are ethane-1-hydroxy-1,1-diphosphonic acid; methanediphosphonic acid; methanehydroxydiphosphonic acid; ethane-1,1,2-triphosphonic acid; propane-1,1,3,3-tetraphosphonic acid; ethane-2-phenyl-1,1-diphosphonic acid; ethane-2-naphthyl-1,1-diphosphonic acid; methanephenyldiphosphonic acid; ethane-1-amino-1,1-diphosphonic acid; methanedichlorodiphosphonic acid; (dichloromethylene diphosphonic acid); nonane-5,5-diphosphonic acid; n-pentane-1,1-diphosphonic acid; methanedifluorodiphosphonic acid; methanedibromodiphosphonic acid; propane-2,2-diphosphonic acid; ethane-2-carboxy-1,1-diphosphonic acid; propane-1-hydroxy-1,1,3-triphosphonic acid; ethane-2-hydroxy-1,1,2-triphosphonic acid; ethane-1-hydroxy-1,1,2-triphosphonic acid; propane-1,3-diphenyl-2,2-diphosphonic acid; nonane-1,1-diphosphonic acid; hexadecane-1,1-diphosphonic acid; pent-4-ene-1-hydroxy-1,1-diphosphonic acid; octadec-9-ene-1-hydroxy-1,1-diphosphonic acid; 3-phenyl-1,1-diphosphonoprop-2-ene; octane-1,1-diphosphonic acid; dodecane-1,1-diphosphonic acid; phenylaminomethanediphosphonic acid; naphthylaminomethanediphosphonic acid; N,N-dimethylaminomethanediphosphonic acid; N-(2,hydroxyethyl)-aminomethanediphosphonic acid; N-acetylaminomethanediphosphonic acid; aminomethanediphosphonic acid; and the pharmaceutically-acceptable salts of these acids, e.g., sodium, potassium, calcium, magnesium, stannous, indium, ammonium, triethanolammonium, diethanolammonium, and monoethanolammonium salts.

Mixtures of any of the foregoing phosphonic acids and/or salts can be used in the practice of this invention.

The geminal diphosphonates of formula (II) are most preferred for use herein.

Ethane-1-hydroxy-1,1-diphosphonic acid, an especially preferred geminal phosphonate, has the molecular formula $CH_3C(OH)(PO_3H_2)_2$ (according to nomenclature by radicals the acid might also be named 1-hydroxyethylidene diphosphonic acid). The most readily crystallizable salt of this acid is obtained when two or three of the acid hydrogens are replaced by sodium. Preferred salts for the purpose of this invention are the trisodium hydrogen salt which has the structure:



and the disodium dihydrogen salt.

The trisodium hydrogen salt normally crystallizes as the hexahydrate which loses some water during air-drying to yield a mixture of the hexa- and monohydrate averaging 3 to 4 molecules of water of hydration.

While any pharmaceutically-acceptable salt of ethane-1-hydroxy-1,1-diphosphonic acid can be used in the practice of this invention, the tetrasodium salt, the trisodium hydrogen salt, the disodium dihydrogen salt, the monosodium trihydrogen salt, and the mixtures thereof are preferred. The other sodium, potassium, ammonium, and mono-, di-, and tri-ethanolammonium salts and mixtures thereof are also suitable, provided caution is observed in regulating the total intake of cation species in the salt composition. These compounds can be prepared by any suitable method; however, an especially preferred method is disclosed in U.S. Patent 3,400,149.

Methanehydroxydiphosphonic acid and related compounds operable herein can be prepared, for example, by the reaction of phosgene with an alkali metal dialkylphosphite. A complete description of these compounds and the method for preparing same is found in U.S. Patent 3,422,137.

Methanediphosphonic acid and related compounds useful herein are

described in detail in U.S. Patent 3,213,030; a preferred method of preparing such compounds is disclosed in U.S. Patent 3,251,907.

Ethane-1,1,2-triphosphonic acid and related compounds which can be used in this invention, as well as a method for their preparation, are fully described in U.S. Patent 3,551,339.

Propane-1,1,3,3-tetraphosphonic acid and related compounds useful herein, and a method for preparing same are fully disclosed in U.S. Patent 3,400,176.

Pentane-2,2-diphosphonic acid and related compounds can be prepared in accordance with the method described by G. M. Kosolopoff in *J. Amer. Chem. Soc.* 75,1500 (1953).

Propane-1,2,3-triphosphonic acid and salts thereof can be prepared by a process disclosed in U.S. Patent 3,743,688.

Butane-1,2,3,4-tetraphosphonic acid and salts thereof can be prepared by a process disclosed in U.S. Patent 3,755,504.

The higher aliphatic vicinal polyphosphonates and salts thereof can be prepared by the process disclosed in U.S. Patent 3,584,035.

Substituted ethane diphosphonic acids and salts and esters thereof are disclosed in U.S. Patent 3,940,436. U.S. Patent 3,944,599 discloses geminal diphosphonate compounds having halogen and hydroxyl substituent groups, and the means for preparing same.

Phosphonobutane tri- and tetra-carboxylic acid compounds and their preparation are disclosed in U.S. Patents 3,886,204 and 3,886,205.

German 2360—798, June 26, 1975, to Henkel & Cie GmbH discloses pharmaceutical and cosmetic preparations for influencing the deposition of poorly soluble calcium salts said preparations comprising polymethylene phosphonic acid compounds. This publication describes the preparation of the phosphonate materials in detail.

The preparation and pharmacological properties of various amino phosphonate compounds are described in German 2343—146 (March 6, 1975); Belgian 822—930 (June 4, 1975); Belgian 822—929 (December 6, 1973); German 2360—711 (June 12, 1975); German 2360—719 (June 6, 1975); Belgian 819—187 (February 26, 1975); Belgian 819—188 (February 26, 1975); and Belgian 819—189 (February 26, 1975).

As can be seen from the foregoing, the preparation of the phosphonates used in the practice of this invention can be accomplished using well-known methods, or by simple modifications of various art-disclosed procedures. Only those organophosphonates which are pharmaceutically acceptable (i.e., provide a satisfactory benefit/risk ratio) are contemplated for use herein. The well-known toxicity of some type (I) monophosphonates (n=1) disclosed in the structural formulas above precludes their use herein. However, such materials are known in the art and are easily avoided in the practice of this invention.

The organosulfoxide compounds of the type used herein are preferably represented by the formula

$$R'R''SO$$

wherein R′ and R″ can be: alkyl; substituted alkyl; hydrocarbyl aryl; substituted hydrocarbyl aryl; heteroaryl; substituted heteroaryl; alkenyl; substituted alkenyl; alkynyl; substituted alkynyl; cyclo-alkyl, alkenyl or alkyoyl; substituted cyclo-alkyl, alkenyl or alkyoyl; hetero-alkyl, alkenyl or alkynyl; or substituted heteroalkyl, alkenyl or alkynyl groups. The substituent groups can be, for example, hydroxyl, alkoxyl and halogen.

Selection of specific organosulfoxides for use with specific organophosphonates can be made using the Skin Penetration Test described more fully hereinafter. This test measures the enhanced penetration of the organophosphonates through the epidermal barrier caused by the organosulfoxides.

Preferred compositions herein are those wherein water comprises a major portion of the penetrating carrier. Accordingly, in such preferred compositions the organosulfoxide must be selected from those which are watersoluble at the intended use concentrations. In general, organosulfoxides wherein R′ and R″ are each C_1—C_{20} alkyl or C_1—C_{20} substituted alkyl groups (i.e., "dialkyl sulfoxides") exhibit substantial solubility in water and are especially preferred in such water-based carriers.

Lower dialkyl organosulfoxides (i.e., R′ and R″ each C_1—C_6 hydrocarbyl or

substituted hydrocarbyl) are known to promote skin penetration when used at solvent concentrations (50%, or more). Such high concentrations can cause undesirable systemic effects. Accordingly, while useful penetrants, the lower dialkyl sulfoxides are not preferred for use herein.

The dialkyl organosulfoxides wherein group R' is a C_6, or higher, alkyl or substituted alkyl group and wherein group R'' is a C_1—C_3 alkyl (especially methyl) or C_1—C_3 substituted alkyl group are preferred herein, since they can be used in less than solvent concentrations.

More preferred are dialkyl organosulfoxides wherein group R' is a C_8, or higher, alkyl or substituted alkyl group and group R'' is C_1—C_3 alkyl (especially methyl) or substituted alkyl, since these can be used at 10%, or less, to provide excellent penetration and are water-soluble at typical use concentrations.

Most preferred herein are the organosulfoxides wherein R' is a C_8—C_{12} alkyl or C_8—C_{12} substituted alkyl group and wherein R'' is methyl. Such materials are highly water-soluble and can be used at concentrations in the range of about 0.1% to about 10% in the compositions herein to provide excellent penetration of the organophosphonate to the site of pathological calcification.

The sulfoxide compounds disclosed herein can be used singly or in combination for the purpose of this invention. These compounds are readily obtainable by well known methods. For example, most can be prepared by the conventional method of first preparing the corresponding thioether and then oxidizing to the sulfoxide. The methods of carrying out these steps have recently been reviewed by A. Schöberl and A. Wagner [Methoden Organischen Chemie (Houben-Weyl), 4th ed., Georg Thieme Verlag, Stuttgart, vol. IX, pp. 97—143, 211—218 (1955)]. Further methods for preparing sulfoxide compounds are disclosed in U.S. Patents 3,288,858; 3,288,859; and 3,288,860.

Non-limiting examples of preferred sulfoxides for use herein include: decyl methyl sulfoxide; octyl hydroxyisopropyl sulfoxide; nonyl ethyl sulfoxide; nonyl methyl sulfoxide; β-hydroxyundecyl methyl sulfoxide; and dodecyl methyl sulfoxide. Decyl methyl sulfoxide is most preferred.

Compositions in accordance with this invention can be formulated with a wide variety of optional dermatologically acceptable ingredients and in a number of liquid or other fluid forms. Compositions according to this invention are "fluid" in its most generic sense; such compositions can be in low viscosity liquid or higher viscosity cream form, can be ointments and can be either solutions, emulsions, or dispersions. The organophosphonate and organosulfoxide ingredients are dissolved in a water-dispersible, dermatologically acceptable vehicle. Such vehicles are well known in the pharmaceutical and cosmetic arts and their choice is not critical to the efficacy of the pharmacologically active substance and the organosulfoxide penetration enhancing agent as long as they are water-miscible. Examples of water-dispersible dermatologically acceptable vehicles are water (highly preferred); water-soluble alcohols (monohydric and polyhydric alcohols, particularly lower C_1—C_8 alcohols, e.g., ethanol, propanol, glycerol, sorbitol, 2-methoxyethanol, diethyleneglycol, monomethy or diethyl ether, ethylene glycol, hexyleneglycol, mannitol, propylene glycol); polyethylene glycols and methoxypolyoxyethylenes (carbowaxes having molecular weight ranging from 200 to 20,000); glyceryl monolaurate, monopalmitate or monostearate; polyoxyethylene glycerols; polyoxyethylene sorbitols; and glucose. When alcohols or their derivatives are used, some water is preferably included since such materials are usually hygroscopic.

Although the vehicle is preferably water-miscible as stated above, petroleum based ointments can also be used. For example, such substances as mineral oil, petroleum jelly, stearoyl diacetin, lanolin, paraffin and beeswax. Although they may tend to slow absorption, they can be used, especially if there is sufficient water-dispersible vehicle present to provide a medium for absorption by animal tissue. Emulsification of such substances also provide a means for their use. Oil-in-water emulsions such as cold cream bases can also be used.

Since the compositions of this invention are to be topically applied to animal tissue, they should be formulated so that they have a pH in aqueous solution of not less than 3.5 nor more than 10.0. Irritation can be encountered at pH's lower than 3.5 and the stability of various ingredients can be adversely affected at pH's higher than 10.0.

The usual buffering materials can be used to adjust the pH to the desired range. Examples of such buffers are: glycine, citric acid, disodium hydrogen phosphate, potassium hydrogen tartrate, potassium hydrogen tartrate, potassium

hydrogen phthalate, and sodium hydrogen succinate. When the salt forms of the organophosphonates are used, buffers generally need not be employed.

The following constitutes a description of the preferred embodiments herein, but various changes and modifications can be made without departing from the spirit and scope of the invention.

Preferred compositions herein comprise from 0.5% to 20%, more preferably from 3% to 12%, of the organophosphonate compound dissolved in the carrier.

Preferred compositions herein are those wherein the carrier comprises from 0.1% to 15%, more preferably 0.2% to 10%, of the organosulfoxide compound, the balance of said carrier comprising a pharmaceutically-acceptable, compatible liquid.

Water is the preferred liquid for dissolving the organosulfoxide to provide the carrier which, in turn, dissolves the organophosphonate compound.

Compositions wherein the organophosphonate compound is a member selected from the group consisting of: ethane-1-hydroxy-1,1-diphosphonic acid, and the pharmaceutically acceptable salts and esters thereof; methanediphosphonic acid, and the pharmaceutically-acceptable salts and esters thereof; and methanedichlorodiphosphonic acid, and the pharmaceutically-acceptable salts and esters thereof, and wherein the organosulfoxide compound is a member selected from the group consisting of: decyl methyl sulfoxide; octyl hydroxyisopropyl sulfoxide; nonyl ethyl sulfoxide; nonyl methyl sulfoxide; β-hydroxyundecyl methyl sulfoxide; and dodecyl methyl sulfoxide, and formulated in the compositional ranges disclosed above are generally preferred for topical application to skin.

Highly preferred compositions herein are homogeneous solutions which consist essentially of from 0.1% to 10% decyl methyl sulfoxide, from 5% to 15% by weight of ethane-1-hydroxy-1,1-diphosphonate, sodium salt form, or methanedichlorophosphonate, sodium salt form, the balance comprising water or water and a water-miscible cosmetic vehicle.

Treatment regimens according to the practice of this invention camprises applying the compositions herein directly to the skin at the situs of pathological calcification. The rate of application and duration of treatment will, of course, depend on the severity of the condition, the response of the particular patient, and such factors as require the sound medical judgment of the attending physician. In general, using the compositions within the compositional ranges noted above, application rates of from 0.0005 g/cm² to 0.10 gm/cm² of afflicted situs per day are used. Application can be done once, or preferably several times daily for periods of a week, or more, to relieve or prevent pathological calcification.

The following Skin Penetration Test demonstrates the penetration of the epidermal barrier by the organosulfoxide/ organophosphonate compositions herein. The organosulfoxide used is the highly preferred n-decyl methyl sulfoxide.

Skin Penetration Test

The ability of organophosphonates to diffuse through the epidermal barrier when applied thereto in compositions falling within the scope of this invention can be measured *in vitro* by various means. A complete description and diagram of suitable apparatus for carrying out such Skin Penetration Tests are fully disclosed in U.S. Patent 3,527,864.

In general terms, a section of skin is placed in a continuous flow apparatus comprising an inner cylindrical chamber mounted within a larger outer cylindrical chamber and sealed thereon with set screws such that water of constant temperature can be introduced into the space between said inner and outer cylindrical chambers and flow around the inner cylindrical chamber and out the constant temperature water outlet. The composition to be tested is placed in the inner chamber in contact with the freshly sectioned piece of skin affixed to the bottom of said inner chamber and resting upon a stainless steel screen support and sealed to a base chamber with a neoprene ring. Ringer's Solution is introduced into the base chamber and is agitated with a magnetic stirring bar which is in contact with the skin. The effluent Ringer's Solution is collected at intervals and measured for penetrants which have diffused through the skin from the test solution. Permeability constants between test (added organosulfoxide penetrant) and control (no organosulfoxide penetrant) can be calculated by methods similar to those employed by Treherne, *J., Invest. Derm.*, 45:249, 1965, and compared to determine the effect of the organosulfoxide on the penetration of the epidermal barrier by the organophosphonate.

In *in vitro* skin penetration tests, a typical organosulfoxide, decyl methyl

sulfoxide, was found to enhance the penetration of a typical organophosphonate, ethane-1-hydroxy-1,1-diphosphonate, some 6-fold over a control.

It will be appreciated from the foregoing that the improved delivery of the organophosphonates through skin provides a novel means for directly treating localized areas of pathological calcification in humans and lower animals in need of such treatment. The following *in vivo* Animal Study supports the effectiveness of this mode of treatment.

Animal Study

The following experiment was carried out to measure the effectiveness of a typical organophosphonate compound, disodium ethan-1-hydroxy-1,1-diphosphonate (EHDP) used in combination with a penetrating carrier comprising a typical organosulfoxide compound, decyl methyl sulfoxide, on dihydrotachysterol (DHT) induced calcification when applied topically.

In general terms, the experiment comprised inducing calciphylaxis in rats by an oral gavage of DHT (10 mg/kg) in a corn oil vehicle (2 mg DHT/ml). After induction of calciphylaxis, subcutaneous administration of ferrous gluconate was used to induce skin calcification. The EHDP composition (10% EHDP, 0.25% decyl methyl sulfoxide, balance water) was topically applied twice daily to the ferrous gluconate injected area at a volume of 0.2 ml/application. Topical application of the EHDP solution was continued on a daily basis for seven days. The animals were then sacrificed and skin samples were submitted for calcium and phosphorus analysis. The percent skin calcium was taken as a measure of the effectiveness of the topical EHDP treatment.

In an animal test of the foregoing type, the base-line control animals without induced calciphylaxis had a percentage skin calcium level of 0.035. In the same test, animals with induced calciphylaxis and saline treatment exhibited a percentage skin calcium of 2.026. In the same test, animals treated with EHDP dissolved in the penetrating carrier vehicle described above had a percentage skin calcium of 0.067.

On the basis of the foregoing, it must be concluded that the topical application of EHDP in the penetrating organosulfoxide carrier to the afflicted situs of the animals substantially reduced the pathological calcification, as compared with control animals.

The following examples further illustrate the practice of this invention, but are not intended to be limiting thereof.

Example I

Ingredient	*% by wt.*
decyl methyl sulfoxide	0.25
EHDP	10.0
Water	Balance

When topically applied to the joints of horses three times daily, the composition of Example I substantially reduces pathological calcification associated with arthritis-like conditions associated with stress at the joints.

In the composition of Example I, the EHDP is replaced by an equivalent amount of the trisodium salt of ethane-1-hydroxy-1,1-diphosphonic acid and equivalent results are secured.

Example II

Ingredient	*% by wt.*
Methanedichlorodiphosphonic acid, disodium salt	12
Decyl methyl sulfoxide	1
Water	Balance

The composition of Example II is topically applied to a situs of pathological calcification in a patient suffering from osteitis deformans. Two mls. of the composition are applied three times daily for a period of one month to alleviate the pathological calcification.

In the composition of Example II, the methanedichlorodiphosphonic acid, disodium salt, is replaced by an equivalent amount of EHDP; methanediphosphonic acid, disodium salt; and methanedichlorophosphonic acid, dimethyl ester; respectively, and equivalent results are secured.

In the composition of Example II the decyl methyl sulfoxide is replaced by an equivalent amount of octyl hydroxyisopropyl sulfoxide, nonyl ethyl sulfoxide, nonyl methyl sulfoxide, β-hydroxyundecyl methyl sulfoxide and dodecyl methyl sulfoxide, respectively, and excellent penetration of the organophosphonate active ingredient through the skin and to the calcified site is secured.

The compositions of Example II are typically applied at the rate of *ca.* 0.002 g on a circular area having a 2 cm. diameter.

Example III

Ingredient	*% by wt.*
Dodecyl methyl sulfoxide	10.0
EHDP	10.0
Ethyl alcohol	10.0
Stearyl alcohol	3.0
Lanolin	6.0
Water	Balance

The composition of Example III provides a cream base penetrating carrier having dissolved therein the organosulfoxide and organophosphonate compounds. The enhanced penetration of the phosphonate compound through the epidermal barrier by virtue of the presence of the organosulfoxide is seen when the penetration of a similarly formulated product without organosulfoxide is compared therewith.

WHAT WE CLAIM IS:—

1. A composition especially adapted for the topical treatment of anomalous mobilization and deposition of calcium phosphate salts in the tissues of humans and lower animals, comprising:

i) a safe and effective amount of an organophosphonate compound; and

ii) a carrier which comprises a safe and effective amount of an organosulfoxide compound, and in which the composition is fluid (as hereinbefore defined) and has a pH in aqueous solution of not less than 3.5 nor more than 10.0.

2. A composition according to Claim 1 wherein the organophosphonate compound is characterized by more than one phosphonate moiety.

3. A composition according to Claim 2 wherein the organophosphonate compound is a diphosphonate.

4. A composition according to Claim 3 wherein the organophosphonate compound is a geminal diphosphonate.

5. A composition according to Claim 1 wherein the organosulfoxide compound is a dialkyl sulfoxide of the formula R'R''SO wherein R' and R'' are each C_1—C_{20} alkyl or C_1—C_{20} substituted alkyl groups.

6. A composition according to Claim 5 wherein the organosulfoxide compound is a dialkyl sulfoxide wherein group R' is a C_6, or higher alkyl or substituted alkyl group and wherein group R'' is a C_1—C_3 alkyl or C_1—C_3 substituted alkyl group.

7. A composition according to Claim 6 wherein the organosulfoxide compound is a dialkyl sulfoxide wherein group R' is a C_6, or higher, alkyl or substituted alkyl group and group R'' is methyl.

8. A composition according to Claim 7 wherein R' is a C_8, or higher, alkyl or substituted alkyl group.

9. A composition according to Claim 8 wherein R' is a C_8—C_{12} alkyl or C_8—C_{12} substituted alkyl group.

10. A composition according to Claim 1 which comprises from 0.5% to 20% by weight of the organophosphonate compound dissolved in the carrier.

11. A composition according to Claim 10 wherein the carrier comprises from 0.1% to 15% by weight of the organosulfoxide compound, the balance of said carrier comprising a pharmaceutically-acceptable, compatible liquid.

12. A composition according to Claim 11 wherein the organophosphonate compound is a member selected from

i) ethane-1-hydroxy-1,1-diphosphonic acid, and the pharmaceutically-acceptable salts and esters thereof;

ii) methanediphosphonic acid, and the pharmaceutically-acceptable salts and esters thereof; and

iii) methanedichlorodiphosphonic acid, and the pharmaceutically-acceptable salts and esters thereof.

13. A composition according to Claim 12 wherein the organosulfoxide compound is selected from decyl methyl sulfoxide; octyl hydroxyisopropyl sulfoxide; nonyl ethyl sulfoxide; nonyl methyl sulfoxide; β-hydroxyundecyl methyl sulfoxide; and dodecyl methyl sulfoxide.

14. A composition according to Claim 13 wherein the organosulfoxide compound is decyl methyl sulfoxide.

15. A composition for the topical treatment of anomalous mobilization and deposition of calcium phosphate salts in the tissues of human and lower animals, substantially as hereinbefore described in any of the Examples.

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